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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,394	08/01/2001	Rosanne M. Crooke	ISPH-0589	4398

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/920,394	Applicant(s) CROOKE ET AL.	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,12-15 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed May 6, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed December 4, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The supplemental information disclosure statement (IDS) submitted on May 6, 2003 was filed after the original IDS on January 28, 2002. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner; however, no translation has been provided for the reference of Toyama et al., which, accordingly, has not been considered.

Response to Amendment

3. Newly amended claim 1 and newly submitted claims 21-23 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: newly amended claim 1 claims antisense sequences that target nucleobases 14 to 1741 of SEQ ID NO: 3. This is a distinct sequence from the originally elected SEQ ID NO: 3, because both 3'

and 5' regions have been omitted. Applicants instant amendment reciting the newly claimed target regions of nucleobases 14 to 1741 of SEQ ID NO: 3 in the instant Request for Continued Examination is examined herein and considered as an election by original presentation. However, subsequent amendments directed to new, specific, and distinct regions of SEQ ID NO: 3 referred to either by region or by nucleobase, will be considered to effectively claim new and distinct targets. Such an amendment would be considered to be drawn to a new invention, because each sequence is distinct and requires a different search, because said search for one target region as originally claimed does not reveal art against another, and furthermore, a search for art against the whole target of the originally claimed target of SEQ ID NO: 3 does not result in a complete and exhaustive list of all art directed against all of applicants newly defined regions. Therefore, as stated above, the instant target sequence of nucleobases 14 to 1741 of SEQ ID NO: 3 is considered to be elected by original presentation for reasons given above.

Regarding new claims 21-23, these are considered to be independent inventions from the originally claimed invention of claims 1, 2, 4-10, and 12-15, because applicants have added new limitations that are unrelated to the invention of the originally filed and examined claims. The new claims are drawn to assay procedures to assess newly claimed levels of antisense mediated inhibition. In the instant case the assays for testing inhibition levels and the levels of inhibition claimed have never been claimed before. Furthermore, a method of administering oligos to cells *in vitro* is distinct from running a northern blot, and also different from performing RT-PCR. Since such assays are necessary to determine specific levels of inhibition as claimed in new claim 21, this claim is also different from a method of administering oligos to cells *in vitro.* Finally, it is a burden upon the Office to search and examine the newly claimed invention

because a search for compounds tested by such assays to determine levels of inhibition are not co-extensive with the search for the compound of claim 1.

Since applicant has received an action on the merits for the originally presented invention, the invention of claims 1, 2, 4-10, and 12-15 has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21-23 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1, 2, and 12 are rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Borg-Capra et al. (WO 01/16358 A2).

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridizes with and inhibits the expression of applicants instant target.

The sequence on page 11 line 2 possesses 100% reverse identity with residues 1697-1721 of the instant application, and would thus specifically hybridize with applicants claimed target region. Although this reference does not specifically teach the function of inhibiting applicants' instant SEQ ID NO: 3 as claimed in the present application, the above-listed compound meets all the structural limitations as set forth in the instant claims. Because the sequence is substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compound is thus considered to possess the functional limitation of specifically hybridizing with and inhibiting the expression of applicants' instant SEQ ID NO: **3**. Support for this conclusion is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound(s) of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence

showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1, 2 and 12 of the instant application are considered anticipated and/or obvious as outlined above.

Claim Rejections - 35 USC § 103

4. Applicant's arguments with respect to claims 1, 2, 4-10 and 12-15 have been considered but most are moot in view of the new ground(s) of rejection. However, those arguments considered relevant to the instant rejection below are addressed at the end of the following rejection.

5. Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (U.S. Patent 5,968,749), or Chang et al. (U.S. Patent 5,484,727), in view of Baracchini et al. (U.S. Patent Number 5,801,154) and Taylor et al (Drug Disc. Today, 1999. 4(12) 562-567.

The claims are drawn to antisense compounds 8-50 nucleobases in length that target nucleobases 14 to 1741 of SEQ ID NO: 3, which is the entire coding region of said SEQ ID NO: 3, and inhibit the expression of ACAT by at least 12%, and to internucleoside, sugar, or nucleobase modifications and chimeras of said antisense compounds, and compositions providing for their *in vivo* use.

Chang et al. (U.S. Patent 5,968,749), or Chang et al. (U.S. Patent 5,484,727; collectively referred to as Chang) teach the sequence of human ACAT and the use of antisense compounds which may be comprised of phosphorothioate linkages to target and inhibit the expression of ACAT (col. 5, lines 1-25 of '727, col. 5, lines 5-30 and claim 2 of 749). Chang do not teach sugar, nucleobase, and 2' modifications, chimeras, and compositions providing for their *in vivo* use.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the coding region corresponding to applicants' recited target region of nucleobases 14 to 1741 of SEQ ID NO: 3, and demonstrate methods of antisense-mediated gene inhibition.

It would have been obvious to one of ordinary skill in the art to make antisense oligos to inhibit ACAT, because the sequence and antisense inhibition of applicants' target had been previously taught by Chang et al. It also would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini et al. into the antisense compounds of Chang et al.

One would have been motivated to create such compounds because Chang et al. expressly teach antisense inhibition of applicants claimed target, and because Chang teaches that ACAT forms a product responsible for atherosclerotic plaques and that inhibiting ACAT would reduce cholesterol intake. Baracchini et al. also teach that the coding region is a preferred target region, which corresponds to the nucleotide region of 14 to 1741 of SEQ ID NO: 3 that is instantly claimed by applicant. One of ordinary skill would have been motivated to incorporate modifications as taught by Baracchini et al., because Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

Furthermore, one would have a reasonable expectation of success of making such oliogs, given that antisense-mediated inhibition of ACAT was previously described by Chang et al., and since modifications to enhance the activity of antisense compounds as taught by Baracchini et al. are routinely performed by one of ordinary skill in the art. Finally, one would have a reasonable expectation of success in using such oligos because Taylor et al. teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

6. Applicants argue that the portion of Chang teaching antisense mediated inhibition is extremely generic, and that it identifies the coding region as a target sequence, and that no specific antisense oligos are taught by Chang, and that what Chang therefore teaches is a method of testing for inhibitory activity of a generic antisense compound.

This is not adopted. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that Chang when viewed individually does not teach the presently claimed invention; however, the test for obviousness is what the *combined* teaching of the prior art would have suggested to those of ordinary skill in the art. Thus, it is not maintained that Chang et al. teach applicants' invention, but the combination of Chang in view of the other cited reference that does. Chang provides very strong motivation by claiming antisense sequences to applicants claimed target, and provides the sequence needed to make such antisense molecules. When this reference is provided with Baracchini, who teaches how to make and use antisense oligos and modifications thereof, it is clear the method of Baracchini is transferable to Chang's sequence using the motivation and structural information of Chang et al. Applicants mischaracterize the Baracchini reference as a generic disclosure; Baracchini actually teaches very specific steps of synthesis and use of antisense inhibitory oligos. The fact that Baracchini does not suggest antisense to applicants instant target is not relevant, because Chang provides such strong motivation. Furthermore, both Chang and Baracchini et al. teach that the coding region is a preferred target region, which is also the region of the instant SEQ ID NO: 3 claimed for

targeting by applicant. Taylor et al. provides the expectation of success, by teaching that one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% using modern techniques available at the time of filing.

Thus, applicants' arguments that Baracchini et al. does not add anything to Chang is simply unsupported, particularly in light of the newly cited Taylor reference that teaches that any gene of known sequence can be inhibited using antisense oligos of the type claimed by applicant.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
July 11, 2003

KAREN LACOURCIERE
PATENT EXAMINER